**Status of the Claims**

Applicants have cancelled claims 4, 5, 7, and 8, and amended claims 1-3, 6, 9-20, 22-26, and 28-30.

Applicants have added claims 31-35. Claims 31-33 are supported by Example 5 of the specification. Claim 34 is supported by Example 3 of the specification. Claim 35 is supported by Example 2 of the specification. No new matter has been added.

Claims 1-3, 6, and 9-35 are under consideration. For the convenience of the Examiner these claims, as amended, are attached as Appendix A.

**Summary of the Office Action**

The Examiner made the following objections and rejections:

(1) Objection to the disclosure because of informalities;

(2) Objection to the specification and rejection of claims 1-30 under 35 U.S.C. § 112, first paragraph;

(3) Rejection of claims 1-30 under 35 U.S.C. § 112, second paragraph; and

(4) Rejection of claims 1-30 under 35 U.S.C. § 103.

These objections and rejections are discussed in order below. Applicants believe that the above amendment and the following remarks respond completely to the objections and rejections.

**(1) Objection to the Disclosure Because of Informalities;**

The Examiner noted several informalities in the disclosure.

Applicants have amended the specification and claims to correct the informalities cited by the Examiner. The word "promotor" has been amended to --promoter-- throughout the specification. The word "glucocorticold" has been amended to --glucocorticoid-- in claim 23. The word "describe" has been amended to --described-- at page 25, line 37. The word "supression" has been amended to --suppression-- at page 9, line 12.

In view of these amendments, Applicants respectfully request reconsideration and withdrawal of the objection to the disclosure because of informalities.

**(2) Objection to the Specification and Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph**

The Examiner objected to the specification and rejected claims 1-30 for lack of enablement. Specifically, the Examiner stated that: (i) the specification does not enable deletion of late genes other than L5, (ii) the specification does not enable adenoviruses from all animal sources, (iii) the specification does not enable adenoviruses in which techniques other than deletion are used to render the designated genes "non-functional," and (iv) the specification does not enable adenoviruses containing any heterologous DNA sequence.

With respect to the deletion of late genes, Applicants respectfully traverse the Examiner's statement that the specification provides no guidance on the deletion of L1-L4 or on the deletion of all the late genes. Applicants note that Example 2 discloses the preparation of recombinant defective adenoviruses in which the sole adenoviral gene is the E4 gene from Ad5 (see Figure 4), and that Example 3 discloses the preparation of recombinant defective adenoviruses in which the sole adenoviral gene is the E2 gene from Ad2 (see Figure 5). Examples 2 and 3 both disclose recombinant adenoviruses in which all of the late genes (L1-L5) have been deleted. In addition, Example 1 discloses the construction of a series of adenovirus deletion mutants. These adenovirus deletion mutants include, *inter alia*, deletions of L3-L5, L1-L4, L1-L3, and L1-L5 (see Figures 1 and 3). Applicants submit that the specification clearly enables the deletion of late genes other than L5, including the deletion of all the late genes.

With respect to the enablement of animal adenoviruses, the specification discloses (at page 5, line 5, to page 6, line 28) that human, animal, and mixed origin adenoviruses have a similar genetic organization, and that Applicants' teachings can be applied to these different types of adenoviruses. Applicants submit, therefore, that the specification does enable the construction of recombinant adenoviruses from human, animal, and mixed sources. In the interest of advancing prosecution, however, Applicants have amended claims 2 and 3 to recite the preferred embodiments of human and canine adenoviruses.

With respect to "non-functional" adenoviral genes, the specification discloses (at page 9, line 8, to page 10, line 23) that viral genes can be rendered non-functional by any of several techniques known to those of skill in the art. Applicants submit, therefore, that the specification does enable the construction of recombinant adenoviruses in which the designated viral genes

have been rendered non-functional by a variety of techniques. In the interest of advancing prosecution, however, Applicants have amended the claims to recite the preferred embodiment in which the designated viral genes have been rendered non-functional by deletion.

With respect to heterologous DNA sequences, Applicants respectfully traverse the Examiner's statement that undue experimentation would be required to construct recombinant adenoviruses having different heterologous DNAs. Applicants first note that the claimed invention is not directed to the heterologous DNAs *per se*, but to recombinant adenoviruses which comprise a heterologous DNA. Applicants' specification discloses, *inter alia*, recombinant adenoviruses which contain a heterologous lac Z gene (see Examples 2 and 3). The specification further discloses that other heterologous DNAs can (at page 6, line 29, to page 9, line 7) and have been (at page 2, lines 10-12) used in recombinant adenoviral constructs. One of ordinary skill in the art would combine Applicants' teachings with his own knowledge about heterologous DNAs, to place any heterologous DNA of interest into the recombinant adenoviruses disclosed by Applicants.

> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

*U.S. v. Teletronics Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

The Examiner has not provided any support, beyond a general statement that genes can differ in origin, function, stability, and size, for the conclusion that undue experimentation would be necessary to construct recombinant adenoviruses comprising any heterologous DNA of interest. Applicants submit that the specification clearly enables the claimed recombinant adenoviruses containing any heterologous DNA.

In view of the above amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the objection to the specification and rejection of the claims under 35 U.S.C. § 112, first paragraph.

**(3) Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph**

The Examiner rejected claims 1-30 as indefinite. Applicants note that claims 4, 5, 7, and 8 have been cancelled.

In the interest of advancing prosecution, Applicants have amended claims 2, 6, 12-14, 17, 19, and 28, to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants respectfully submit that these claims, as amended, are not indefinite.

Applicants submit that the other pending claims are also not indefinite, because their meaning would be understood by one possessing ordinary skill in the art and having Applicants disclosure.

> (T)he definiteness of the language employed must be analyzed-- not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.

*In re Moore*, 169 USPQ 236, 238 (CCPA 1971).

The Examiner stated that claims 1, 7, and 8 are indefinite because it is not clear which sequences are encompassed by the term "heterologous DNA sequence." Applicants note that claims 7 and 8 have been cancelled, but that this term is also recited in new claims 31, 34, and 35. Applicants submit that claims 1, 31, 34, and 35 are not indefinite for reciting the term "heterologous DNA sequence," because Applicants disclose this term in the specification at page 6, line 29 to page 9, line 7, and also because the meaning of this term is well known to one of ordinary skill in the art. Applicants also point out, as discussed in (2) above, that the claimed invention is not directed to the heterologous DNAs *per se*, but to recombinant adenoviruses which comprise a heterologous DNA. One of ordinary skill in the art would combine Applicants' teachings with his own knowledge about heterologous DNAs, and understand the claims to recite any heterologous DNA of interest placed in the recombinant adenoviruses disclosed by Applicants.

With respect to claim 3, Applicants submit that this claim is not indefinite for reciting the phrase "human group C adenovirus," because the meaning of this term is well known to one of ordinary skill in the art. Applicants submit, as Appendix B, a discussion of the classification of human adenoviruses from J. Tooze, DNA Tumor Viruses, pp. 388-89, Cold Spring Harbor Laboratory, 2d Ed. Revised, 1981. This reference describes how human adenoviruses have been classified into groups ("subgroups") based on their oncogenicity. Applicants' specification also discloses the human adenoviruses of the present invention, at page 5, lines 13-17.

The Examiner stated that claims 15 and 16 are indefinite for reciting the terms "antigenic peptide" and "tumors," that claim 18 is indefinite for reciting the terms "a signal sequence" and "secretory pathways," and that claim 30 is indefinite for reciting the term "a vehicle." Applicants submit that the meaning of these terms is understood by those having ordinary skill in the art, especially in view of Applicants' disclosure at page 8, lines 6-15, at page 9, lines 1-7, and at page 12, lines 14-29.

In view of the above amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, second paragraph.

**(4) Rejection of the Claims Under 35 U.S.C. § 103**

Applicants traverse the rejection of claims 1-30 as obvious over Davis, in combination with Berkner, Bajocci, Weinberg, and James. Applicants submit that the combination of cited references do not teach or suggest Applicants' claimed invention.

Applicants Claimed Invention:

The present invention relates to defective recombinant adenoviral vectors. While adenoviral vectors have been described in the prior art, the prior art vectors all have various disadvantages, including the production of replication competent virus, the expression of numerous viral genes, and/or a limited capacity for foreign DNA. Applicants' claimed invention overcomes these disadvantages by providing recombinant adenoviruses which are replication defective, which have multiple deletions in the adenoviral genome, and which have the capacity to accept large heterologous DNA sequences.

Specific embodiments of Applicants' claimed invention include:

(a) A defective recombinant adenovirus comprising;

-the ITR sequences,

-an encapsulation sequence, and

-a heterologous DNA sequence,

wherein the E1 gene has been rendered non-functional by deletion, and wherein the E2 or E4 genes have been rendered non-functional by deletion;

(b) A defective recombinant adenovirus comprising;
-the ITR sequences,
-an encapsulation sequence, and
-a heterologous DNA sequence,
wherein the E3 and E4 genes have been rendered non-functional by deletion;

(c) A defective recombinant adenovirus consisting essentially of;
-the ITR sequences,
-an encapsulation sequence,
-a heterologous DNA sequence, and
-all or part of the E2 gene; and

(d) A defective recombinant adenovirus consisting essentially of;
-the ITR sequences,
-an encapsulation sequence,
-a heterologous DNA sequence, and
-all or part of the E4 gene.

Applicants' claimed invention also relates to cell lines used to prepare the defective recombinant adenoviral vectors.

Discussion of the Cited References:

**Davis** describes methods and vaccines for the production of antibodies using live infectious recombinant adenoviruses. Davis provides an oral enteric coated dosage form of live infectious adenovirus which has been engineered to contain genes encoding foreign antigens. Upon release in the intestine these viruses reproduce and express the foreign antigens, thereby inducing immunity.

Davis does not teach replication defective recombinant adenoviruses. In fact, Davis teaches that if a foreign gene is inserted into a region which is essential for adenovirus replication, then an infectious helper virus must be co-administered in order to permit replication of the recombinant virus (at column 9, lines 43-57). This major difference between what is disclosed by Davis and what is claimed by Applicants may be seen by referring to Appendix C, which shows the replication cycle of a replication-competent adenovirus. Whereas Davis discloses a system in which steps 1-5 of the viral life cycle must occur, Applicants' invention is directed to a system in which only step 1 occurs.

In effect, Davis "teaches away" from Applicants' invention by emphasizing the necessity of viral replication. Statements in a prior art reference which teach away from the claimed invention are indicia of non-obviousness. Gillette Co. v. S.C. Johnson & Son, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990).

**Berkner** is a review of the state of development of adenoviral vectors for the expression of heterologous genes. Berkner discloses that nonconditional helper-independent viruses can be generated by insertions in E3 or other nonessential regions, and that conditional helper-independent viruses can be generated by insertions in E1 or E4. These are first generation adenoviral vectors, which have the many disadvantages disclosed in the specification at page 2, lines 12-27. Berkner also discloses defective adenoviral vectors in which the gene of interest is joined to the SV40 T antigen, and the virus is passaged in CV-1 cells.

Berkner does not teach one of skill in the art how to make or use the recombinant adenoviral vectors of the present invention. At most, Berkner provides wishful thinking and an invitation to experiment. Berkner speculates (at page 620) that *potential deletions* in E4 *may* permit larger gene inserts. Berkner suggests (at page 621) that all that is required in *cis* are the ITRs and a packaging sequence, and that this approach has the *potential* for enabling large substitutions. Berkner comments however (at page 617), that while plasmids containing the ITRs could *theoretically* be used to generate recombinants with large inserts "(t)his approach however, has not yet been developed." Berkner's speculations and wishful thinking would clearly not have suggested to one of ordinary skill in the art that Applicants' claimed invention should be carried out and would have a reasonable likelihood of success.

**Bajocci** discloses replication defective recombinant adenoviral vectors in which a heterologous gene replaces part of E1 and in which a portion of E3 is deleted. Bajocci does not teach or suggest that any other regions of the viral genome should or can be deleted.

**Weinberg** discloses a cell line (W162) which contains an adenoviral E4 gene and which supports the replication of an E4 adenoviral deletion mutant. Weinberg does not disclose cell lines that complement any other viral functions, nor cell lines that complement multiple viral functions, nor cell lines comprising complementing genes under the control of inducible promoters.

**James** is a review of antiviral antisense and ribozyme technology. James discloses that antisense RNA can be delivered into cells using microinjection, calcium phosphate co-precipitates, electroporation, DEAE-Dextran complexes, or transducing vectors based on retroviruses. James does not disclose the use of adenoviral vectors or cells used to prepare adenoviral vectors.

The Combination of Cited References Does Not Suggest Applicants' Invention

To establish a case of *prima facie* obviousness, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. *In re Dow Chemical Company*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

In the present case, the cited references provide neither the suggestion to make Applicants' claimed invention nor a reasonable expectation of success. Davis teaches replication competent adenoviruses which express foreign antigens. Davis does not teach how to make or use any replication defective adenoviral vectors having multiple deletions in the viral genome. Berkner does not remedy the deficiencies of Davis. Berkner discloses the use of first generation adenoviral vectors and of a specialized system using the SV40 T antigen and CV-1 cells. While Berkner speculates that further deletions could be made in the viral genome, and speculates on the use of plasmids containing viral ITRs, she does not suggest how these speculations could be carried out or provide one of skill in the art with a reasonable expectation of success. Bajocci, Weinberg, and James do not remedy these deficiencies. Bajocci does not teach or suggest that any regions other than E1 or E3 can or should be deleted from the viral genome. Weinberg does not disclose cell lines that can complement any viral functions other than E4. James does not discuss adenoviral vectors at all. None of these references teach or suggest, either alone or in combination, how to make or use Applicants' claimed adenoviral vectors and cell lines.

In view of the above remarks, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

In view of the above amendments and remarks, Applicants respectfully submit that this application is in condition for allowance. Favorable reconsideration and an action passing this case to issue are respectfully requested.

in the event that a telephone interview would be helpful in advancing the prosecution of this application, Applicants' agent invites the Examiner to contact her at the number provided below.

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Respectfully submitted,

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Appendix A
U.S. Serial No. 08/397,225
DEFECTIVE ADENOVIRUS VECTORS AND
USE THEREOF IN GENE THERAPY
Claims after amendment mailed 06 May 1996

1. (Amended) A defective recombinant adenovirus comprising;
-the ITR sequences,
-an encapsulation sequence, and
-a heterologous DNA sequence,
wherein the E1 gene has been rendered non-functional by deletion, and wherein the E2 or E4 genes have been rendered non-functional by deletion.

2. (Amended) An adenovirus according to claim 1, characterized in that the adenovirus sequences are from a canine adenovirus.

3. (Twice Amended) An adenovirus according to claim 1, characterized in that the adenovirus sequences are from a human group C adenovirus.

6. (Twice Amended) An adenovirus according to claim 1, characterized in that the late genes L1-L5 have been rendered non-functional by deletion.

9. (Amended) An adenovirus according to claim 1, characterized in that the E3 gene has been rendered non-functional by deletion.

10. (Amended) An adenovirus according to claim 9, characterized in that the L5 gene has been rendered non-functional by deletion.

11. (Twice Amended) An adenovirus according to claim 1, further comprising a functional E3 gene under the control of a heterologous promoter.

12. (Twice Amended) An adenovirus according to claim 1, characterized in that the heterologous DNA sequence is selected from the group consisting of therapeutic genes and genes encoding antigenic peptides.

13. (Twice Amended) An adenovirus according to claim 12, characterized in that the heterologous DNA is a therapeutic gene which encodes a product selected from the group consisting of enzymes, blood derivatives, hormones, lymphokines, growth factors, neurotransmitters, precursors of neurotransmitters, synthetic enzymes, trophic factors, apolipoproteins, dystrophin, minidystrophin, tumor suppressor genes, and genes encoding factors involved in coagulation.

14. (Amended) An adenovirus according to claim 1, characterized in that the heterologous DNA encodes an antisense sequence.

15. (Amended) An adenovirus according to claim 12, characterized in that the heterologous DNA encodes an antigenic peptide capable of generating an immune response against microorganisms, tumors, or viruses.

16. (Amended) An adenovirus according to claim 15, characterized in that the gene encodes an antigenic peptide specific for a virus selected from the group consisting of the Epstein Barr virus, the HIV virus, the hepatitis B virus, and the pseudo-rabies virus.

17. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a promoter.

18. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a signal sequence.

19. (Twice Amended) A cell line comprising, integrated into its genome, the genes necessary to complement a defective recombinant adenovirus according to claim 1, wherein one of the complementing genes is under the control of an inducible promoter.

20. (Twice Amended) A cell line according to claim 19, characterized in that it comprises, in its genome, an E1 gene and an E2 gene wherein the E2 gene is under the control of an inducible promoter.

21. (Amended) A cell line according to claim 20, characterized in that it additionally comprises the E4 gene from an adenovirus.

22. (Twice Amended) A cell line according to claim 19, characterized in that it comprises, in its genome, an E1 gene and an E4 gene wherein the E4 gene is under the control of an inducible promoter.

23. (Twice Amended) A cell line according to claim 19, further comprising a glucocorticoid receptor gene.

24. (Twice Amended) A cell line according to claim 19, characterized in that it comprises E2 and E4 genes and the E2 and E4 genes are under the control of an inducible promoter.

25. (Amended) A cell line according to claim 19, characterized in that the inducible promoter is the LTR promoter of MMTV.

26. (Twice Amended) A cell line according to claim 19, characterized in that it comprises a gene encoding the 72 K protein of E2.

27. (Amended) A cell line according to claim 19, characterized in that it is obtained from the line 293.

28. (Twice Amended) A composition comprising a defective recombinant adenovirus according to claim 1 and a pharmaceutically acceptable vehicle.

29. (Twice Amended) A composition comprising a recombinant adenovirus according to claim 10 and a pharmaceutically acceptable vehicle.

30. (Twice Amended) A composition according to claim 28 wherein the vehicle is pharmaceutically acceptable for an injectable formulation.

31. A defective recombinant adenovirus comprising;

-the ITR sequences,

-an encapsulation sequence, and

-a heterologous DNA sequence,

wherein the E3 and E4 genes have been rendered non-functional by deletion.

32. An adenovirus according to claim 31, characterized in that the late genes L1-L5 have been rendered non-functional by deletion.

33. A cell line according to claim 19, characterized in that it comprises the open reading frames ORF6 and ORF6/7 of E4.

34. A defective recombinant adenovirus consisting essentially of;

-the ITR sequences,

-an encapsulation sequence,

-a heterologous DNA sequence, and

-all or part of the E2 gene.

35. A defective recombinant adenovirus consisting essentially of;

-the ITR sequences,

-an encapsulation sequence,

-a heterologous DNA sequence, and

-all or part of the E4 gene.